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Cigarette Smoking and Cancer Mortality Risk in Japanese Men and Women—Results from Reanalysis of the Six-Prefecture Cohort Study Data

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In 1965 a cohort of 265,000 residents of 29 public health districts in six prefectures throughout Japan was established and followed between 1966 and 1981. By using survival analysis based on Poisson regression models adjusted for age, prefecture of residence, and occupation, a statistically significant dose-response relationship between cigarette smoking and mortality rate was found for cancers of the liver, pancreas, and lung in both sexes; cancers of the oral cavity, esophagus, stomach, larynx, and bladder in men; and cancer of the uterus in women. The magnitudes of relative risks were only slightly affected by adjustment for prefecture of residence or occupation. Analysis using linear relative risk models revealed that the inclusion of a quadratic term for the amount of daily cigarette consumption in addition to the linear term improved the fit of the model significantly for cancers of the esophagus and stomach in men and cancer of the stomach in women. The sex ratio of gastric cancer mortality was higher among smokers than among nonsmokers. When the follow-up period was divided into four 4-year intervals, it was noted that the relative mortality risk associated with lung cancer among males increased significantly during these time periods.

Introduction

A cohort of 265,000 residents, aged 40 or over, from 29 public health districts in six prefectures throughout Japan was followed during the period of 1966 to 1981, and the results from this cohort study have been published in many reports, including the proceedings of the conference on Statistical Methods in Cancer Epidemiology held at Hiroshima Laboratory of the Radiation Effects Research Foundation in 1984 (*1*). In the analysis of mortality experience of this cohort, however, survival analysis accounting for multiple covariates has not been conducted so far. Recently, reanalysis of the data using such up-to-date statistical methods has started. This paper presents the results of reanalysis on the site-specific cancer risk associated with smoking.

Study Population

From October to December 1965, public health nurses conducted a questionnaire survey of all the residents aged 40 or older in 29 public health districts in six selected Japanese prefectures (Miyagi, Aichi, Osaka, Hyogo, Okayama, and Kagoshima). The prefectures were selected because they geographically represent the entire country, and all but Kagoshima had prefectural cancer registration systems (*1*). Respondents to the survey numbered 122,261 men and 142,857 women. The proportion of the respondents, obtained from a calculation based on the 1965 National Census population, were 94.8% total and 99.8, 91.4, 91.3, 93.8, 95.2, and 99.2% in the prefectures of Miyagi, Aichi, Osaka, Okayama, Hyogo, and Kagoshima, respectively. The age and sex distribution of the respondents have been reported elsewhere (*1*). A one-page questionnaire was used in the survey to obtain information on factors such as smoking, drinking, and dietary habits, occupation, and marital status. The inquiry regarding smoking history was answered by 98% of the respondents, and the amount of daily cigarette consumption was unknown except for only 6% of the current, daily cigarette smokers.

At the beginning of each follow-up year, a migration survey was conducted through reference to the local residence registration, and those who were found to have migrated out from the residential public health districts during the previous year were excluded from the mortality follow-up. During the 16-year follow-up period, 8% of the respondents migrated out from the original districts. The deaths were annually ascertained through checking against vital statistics kept at each

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public health center. The causes of death were coded by T. Hirayama, using the *7th Revision of the International Classification of Diseases (ICD-7)*. Excluded from the analysis were 8% of the total subjects, who were exsmokers, occasional smokers, and those for whom age or smoking history information was unavailable.

Statistical Methods

The person-years and the numbers of cancer cases were aggregated and stratified by sex, 5-year intervals of attained age, four follow-up intervals (1966–69, 1970–73, 1974–77, 1978–81) and six categories of daily cigarette consumption (0, 1–4, 4–14, 15–24, 25–34, 35+) for men and four categories (0, 1–4, 5–14, 15+) for women. In some analyses the data were further stratified by prefecture of residence and occupation.

Let i be the stratum in the cross-classification of city, sex, age and follow-up interval and let j be the exposure (amount of cigarettes consumed per day) category. The mortality rate M_{ij} for stratum i and dose group j can then be defined as

$$M_{ij} = M_{i0}{*}\mathrm{RR}_{ij}$$

where RR_{ij} is the risk in stratum i of exposure group j, relative to the 0 exposure group (nonsmokers). Unless otherwise specified, the analyses reported here are based on linear relative risk (RR) models of the form

$$\mathrm{RR}_{ij} = 1 + \beta D_{ij}$$

where D_{ij} is the stratum-specific average daily cigarette consumption for exposure group j. Also used in some analyses were the loglinear RR models of the form

$$\mathrm{RR}_{ij} = \exp\left(\sum^{j} \beta_j G_{ij}\right)$$

where G_{ij} is the dummy variable (takes 0 or 1) for exposure group j.

Parameters were estimated by the method of maximum likelihood, (*10*) assuming that the numbers of deaths Y_{ij} are independent Poisson random variables with the expected values

$$E(Y_{ij}) = PY_{ij}{*}M_{i0}{*}\mathrm{RR}_{ij}$$

where PY_{ij} is the person-years for stratum i and exposure group j. A more detailed description of the statistical methods is available elsewhere (*2*).

Results

During 1966 to 1981, 12,357 cancer deaths were identified from among the cohort members included in this analysis. The cancer site-specific relative mortality risks (RRs) associated with daily cigarette consumption were obtained from survival analysis based on Poisson regression models. The data were cross-classified by prefecture of residence and occupation in addition to attained age and follow-up interval, and the procedure yielded the strata of 1062 for males and 1037 for females after exclusion of the cells with no person-year. The background mortality rates were permitted to vary without restriction among them.

The positive linear trend of RRs in men was statistically significant, by two-sided tests, for cancers of the oral cavity (*ICD-7* 140–148), esophagus, stomach, liver, pancreas, larynx, lung, and bladder in men (Table 1). After adjustment for alcohol consumption, the observed association with liver cancer changed only slightly while the RRs for cancers of the oral cavity, and esophagus became a little smaller. It should be noted that there were statistically nonsignificant elevations of the RRs for cancers of the colon and prostate in the group smoking 35 or more cigarettes per day. In women (Table 2) RRs increased with larger daily cigarette consumption for cancers of the liver, pancreas, lung, and uterus. Also associated with cigarette smoking was cancer of the esophagus, although the linear trend was statistically nonsignificant.

The RRs in both men and women changed only slightly when the data were not stratified by either prefecture of residence or occupation. Neither did use of a parametric background model, assuming a loglinear effect of attained age, affect the RRs. In the following analysis the prefecture of residence and occupation were not taken into account, and the effect of attained age was adjusted for by a parametric background model which assumes a loglinear effect of attained age unless otherwise specified.

Next, dose-response relationships between site-specific cancer mortality and daily cigarette consumption were examined by survival analysis using linear RR models. The analysis revealed that the inclusion of a quadratic term for the amount of daily cigarette consumption in addition to the linear term significantly improved the fit of the models for cancer of the esophagus ($p = 0.02$) and stomach ($p < 0.01$) in men and for cancer of the stomach ($p = 0.02$) in women. The coefficients of the quadratic term were all negative.

Among nonsmokers, significantly higher mortality was observed in men than in women for cancers of the esophagus, stomach, liver, and bladder (Table 3). The sex ratio of the mortality rate did not change significantly by inclusion of smokers smoking 1 to 24 cigarettes per day, except for stomach cancer, for which the sex ratio tended to rise as the smoking dose increased. The RR of lung cancer was somewhat different between the two sexes, namely 3.4 and 2.7 at 10 cigarettes per day for men and women, respectively, but the difference was statistically nonsignificant ($p > 0.1$). The smokers of 25 or more cigarettes per day were excluded from these analyses because of the paucity of female subjects in this group.

RRs at 10 cigarettes per day were calculated for each 4-year interval (Table 4) using a linear RR model. Those who attained age 80 or older in the respective follow-up intervals were excluded from the analysis to avoid the possible effects on time trend from inaccurate di-

Table 1. Cigarette smoking and cancer mortality in Japanese males.

Cancer site		Daily cigarette consumption							p for trend	p for heterogeneity
		Never smoked	1–4	5–14	15–24	25–34	35+	1+		
Oral cavity[a]	Number	8	0	25	32	5	2	64	0.002	0.05
	RR[b]	1.0[c]	2.2	(1–14/day)	2.7	4.2	4.0	2.5		
	95%CI[b]	—	1.0–5.2		1.3–6.3	1.3–12.8	0.6–16.2	1.3–5.7		
Esophagus	Number	47	3	127	164	13	7	314	< 0.001	< 0.001
	RR	1.0	0.9	2.0	2.4	2.1	2.5	2.2		
	95%CI	—	0.2–2.5	1.4–2.8	1.7–3.3	1.1–3.8	1.0–5.2	1.6–3.0		
Stomach	Number	491	49	994	1144	105	56	2348	< 0.001	< 0.001
	RR	1.0	1.4	1.4	1.5	1.4	1.7	1.5		
	95%CI	—	1.0–1.8	1.3–1.6	1.4–1.7	1.1–1.7	1.3–2.2	1.3–1.6		
Colon	Number	43	3	62	69	8	5	147	> 0.1	> 0.1
	RR	1.0	0.9	1.0	1.1	1.2	1.8	1.1		
	95%CI	—	0.2–2.6	0.7–1.6	0.7–1.6	0.5–2.4	0.6–4.2	0.8–1.5		
Rectum	Number	50	5	85	101	10	3	204	0.09	> 0.1
	RR	1.0	1.4	1.3	1.4	1.5	1.1	1.4		
	95%CI	—	0.5–3.2	0.9–1.9	1.0–2.0	0.7–2.9	0.3–2.9	1.0–1.9		
Liver	Number	106	8	240	254	29	15	546	0.002	0.002
	RR	1.0	1.1	1.6	1.4	1.6	1.9	1.5		
	95%CI	—	0.5–2.0	1.3–2.0	1.2–1.8	1.1–2.4	1.1–3.2	1.2–1.9		
Gall bladder	Number	35	6	61	70	6	3	146	> 0.1	> 0.1
	RR	1.0	2.6	1.4	1.4	1.3	1.5	1.4		
	95%CI	—	1.0–5.9	0.9–2.1	0.9–2.1	0.5–2.9	0.4–4.1	1.0–2.0		
		AR (%) = 22								
Pancreas	Number	54	4	112	137	10	5	268	0.04	0.07
	RR	1.0	1.1	1.5	1.6	1.2	1.3	1.5		
	95%CI	—	0.3–2.7	1.1–2.1	1.2–2.2	0.6–2.2	0.4–2.9	1.1–2.1		
Larynx	Number	1	1	23	35	9	4	72	< 0.001	< 0.001
	RR	1.0	13.7	17.0	25.7	76.9	73.4	23.8		
	95%CI	—	0.5–346	3.6–304	5.5–458	14–1427	11–1444	5.3–420		
Lung	Number	80	14	361	629	76	40	1120	< 0.001	< 0.001
	RR	1.0	2.5	3.3	5.4	7.1	8.4	4.5		
	95%CI	—	1.4–4.3	2.6–4.3	4.3–6.9	5.1–9.7	5.7–12.3	3.6–5.7		
Prostate	Number	39	8	50	42	3	5	108	> 0.1	0.03
	RR	1.0	3.1	1.0	0.9	0.8	3.0	1.1		
	95%CI	—	1.4–6.4	0.7–1.6	0.6–1.4	0.2–2.1	1.0–7.1	0.7–1.5		
Bladder	Number	24	3	43	66	5	3	120	0.005	0.07
	RR	1.0	1.8	1.4	2.0	1.7	2.1	1.7		
	95%CI	—	0.4–5.0	0.9–2.3	1.3–3.3	0.6–4.1	0.5–6.1	1.1–2.7		

[a] *Seventh Revision of the International Classification of Diseases*, 140–149.
[b] Relative risk (RR) and 95% confidence interval (95%CI), obtained from a Poisson regression analysis. The data were stratified by prefecture of residence, occupation, attained age (5-year interval), and observation period (1966–1969, 1970–1973, 1974–1977, 1978–1981).
[c] Reference category.

agnosis in those older subjects. The linear trend became sharper in later follow-up periods only for cancer of the lung in men. For lung cancer in females, a similar trend was also noted but was not statistically significant.

The RRs for six smoking categories of men for each follow-up interval are shown in Tables 5 and 6. A slight decrease of background rate in the 1978 to 1981 period cannot entirely account for the increase of the RRs during the follow-up period. When the dose-response relationship for lung cancer in males was examined for each follow-up interval separately, the addition of the quadratic term for the amount of daily cigarette consumption to the linear term significantly improved the fit of the model in the first two intervals (1966–1969 and 1970–1973) but did not in the last two intervals (1974–1977 and 1978–1981). The coefficients of the quadratic term were all negative.

The time trends of the RRs were still evident when the data were stratified by attained age (Table 7) and occurred in the mid-1970s regardless of the age at the start of the follow-up (data not shown). The magnitudes of the change in the RRs during the follow-up period was a little higher in farmers and white collar workers than blue collar workers, but the difference was statistically nonsignificant.

Discussion

The RRs obtained from survival analysis based on Poisson regression models were similar to earlier results obtained from nonsurvival analysis (*1,3*). These

Table 2. Cigarette smoking and cancer mortality in Japanese females.

Cancer site		Daily cigarette consumption						
		Never smoked	1–4	5–14	15+	1+	p for trend	p for heterogeneity
Oral cavity	Number	35	1	3	1	5	> 0.1	> 0.1
	RR[a]	1.0[b]	1.7	1.1	2.3	1.3		
	95%CI[a]	—	0.1–7.9	0.3–3.1	0.1–10.9	0.5–3.2		
Esophagus	Number	104	4	20	0	24	> 0.1	0.08
	RR	1.0	1.8	1.7 (5+/day)		1.7		
	95%CI	—	0.5–4.3	1.0–2.7		1.1–2.7		
Stomach	Number	1394	31	146	16	193	> 0.1	0.04
	RR	1.0	1.2	1.3	0.8	1.2		
	95%CI	—	0.8–1.7	1.1–1.5	0.5–1.3	1.0–1.4		
Colon	Number	232	5	18	2	25	> 0.1	> 0.1
	RR	1.0	1.1	0.9	0.5	0.9		
	95%CI	—	0.4–2.4	0.5–1.4	0.1–1.6	0.6–1.3		
Rectum	Number	189	2	14	6	22	> 0.1	> 0.1
	RR	1.0	0.5	0.9	2.1	0.9		
	95%CI	—	0.1–1.7	0.5–1.5	0.8–4.3	0.6–1.5		
Liver	Number	334	9	42	13	64	0.001	0.008
	RR	1.0	1.4	1.4	2.5	1.6		
	95%CI	—	0.7–2.5	1.0–2.0	1.3–4.1	1.2–2.0		
Gall bladder	Number	207	7	22	6	35	0.06	> 0.1
	RR	1.0	1.8	1.3	1.8	1.4		
	95%CI	—	0.8–3.5	0.8–1.9	0.7–3.8	1.0–2.0		
Pancreas	Number	198	2	28	4	34	0.02	0.03
	RR	1.0	0.6	1.9	1.4	1.6		
	95%CI	—	0.1–1.9	1.2–2.8	0.4–3.4	1.1–2.3		
Larynx	Number	12	0	3	0	3		
	RR	1.0	—	—	—	1.8		
	95%CI	—	—	—	—	0.4–6.0		
Lung	Number	303	11	65	15	91	< 0.001	< 0.001
	RR	1.0	1.9	2.5	3.1	2.5		
	95%CI	—	1.0–3.2	1.9–3.3	1.8–5.1	2.0–3.2		
Bladder	Number	52	1	11	1	13	0.07	> 0.1
	RR	1.0	0.9	2.2	1.2	1.9		
	95%CI	—	0.1–4.0	1.1–4.1	0.1–5.7	1.0–3.4		
Breast	Number	182	2	17	3	22	> 0.1	> 0.1
	RR	1.0	0.6	1.1	1.0	1.0		
	95%CI	—	0.1–2.0	0.6–1.8	0.2–2.6	0.6–1.6		
Cervix uteri	Number	61	1	4	5	10	0.09	0.05
	RR	1.0	0.8	0.7	4.6	1.3		
	95%CI	—	0.1–3.8	0.2–1.8	1.6–10.6	0.6–2.4		
Ovary	Number	83	1	8	3	12	> 0.1	> 0.1
	RR	1.0	0.7	1.3	2.4	1.3		
	95%CI	—	0.1–3.3	0.6–2.5	0.6–6.6	0.7–2.4		
Uterus[c]	Number	452	13	55	13	81	0.02	< 0.001
	RR	1.0	1.5	1.4	1.6	1.4		
	95%CI	—	0.8–2.5	1.0–1.8	0.9–2.8	1.1–1.8		

[a] Relative risk (RR) and 95% confidence interval (95%CI) obtained from a Poisson regression analysis. The data were stratified by prefecture of residence, occupation, attained age (5-year interval), and observation period (1966–1969, 1970–1973, 1974–1977, 1978–1981).
[b] Reference category.
[c] Cancer of uterus, including 11 cases of cancer of the uterine corpus that were observed only among nonsmokers.

results were similar even when the current results were compared with previous results, which did not take into account the prefecture of residence or occupation. As reported previously, the population-attributable risks were also similar between the results from the two different analyses (*4*).

The cancer sites having a relationship with smoking confirmed in this analysis included cancers of the oral cavity, esophagus, lung, larynx, pancreas, and bladder. These cancers were also concluded to be associated with smoking in the U.S. Surgeon General's report (*3*).

A weak association between gastric cancer and smoking, which was noted by the Surgeon General (*3*), was confirmed in this analysis. An interesting fact about the results on gastric cancer was the higher sex ratio of the risk among smokers than among nonsmokers. Although

Table 3. Sex ratio of the mortality rate.

Cancer site	Never smoked	Daily cigarette consumption[a] 1–4	5–14	15–24	Total	LRS[b]
Esophagus						
Ratio[c]	2.1	1.0	1.9		2.0	1.0
95% CI[c]	1.6–2.0	1.3–3.3	1.7–2.4		1.5–2.6	
Stomach						
Ratio	1.7	2.1	2.0	4.0	1.9	13.9
95% CI	1.5–1.9	1.4–3.3	1.7–2.4	2.4–7.3	1.7–2.0	
Liver						
Ratio	1.6	1.2	1.7	.9	1.5	4.0
95% CI	1.3–2.0	0.5–3.1	1.2–2.4	0.5–1.6	1.3–1.8	
Pancreas						
Ratio	1.4	2.7	1.2	1.6	1.3	1.1
95% CI	1.0–1.8	0.5–19.6	0.8–1.9	0.7–5.1	1.1–1.7	
Lung						
Ratio	1.3	1.7	1.7	2.2	1.5	4.9
95% CI	1.0–1.7	0.8–3.9	1.3–2.2	1.4–4.1	1.3–3.8	
Bladder						
Ratio	2.1	4.0	1.2	3.1	1.9	2.7
95% CI	1.4–3.8	0.5–80.4	0.6–2.4	0.7–	1.3–2.8	

[a] Mean cigarette consumption per day for the categories 1–4, 5–14, and 15–24 were 3, 9, and 18, respectively, for men; and 3, 8, and 18, respectively, for women.
[b] Likelihood ratio statistics (LRS) for the heterogeneity of sex ratios among the four smoking categories (df = 3). For cancer of the esophagus the degree of freedom is 2.
[c] Sex ratios (ratios) and 95% confidence intervals (95%CI) were obtained from Poisson regression analysis of the data stratified on attained age and follow-up intervals. The 95% CI was left blank when no feasible value was obtained.

Table 4. Relative risk (RR) for smoking and cancer follow-up periods.

Cancer site	Sex	Period 1966–1969	1970–1973	1974–1977	1978–1981	LRS for heterogeneity[a]
Esophagus	Male	1.6[b]	1.8	1.4	1.7	1.0
	Female	0.9	1.0	2.6	2.4	2.6
Stomach	Male	1.1	1.3	1.3	1.2	7.3
	Female	1.0	1.5	1.1	1.0	4.3
Liver	Male	1.3	1.3	1.4	1.0	5.6
	Female	1.7	1.4	2.0	1.3	1.3
Pancreas	Male	1.7	1.1	1.2	1.3	1.8
	Female	2.7	1.2	1.2	1.6	1.8
Lung	Male	2.4	2.5	3.0	5.4	9.0
	Female	1.5	2.9	2.9	3.0	3.2
Bladder	Male	1.5	0.9	2.0	1.4	4.0
	Female	2.3	1.1	4.3	2.3	2.0
All cancer	Male	1.2	1.3	1.5	1.4	16.1
	Female	1.3	1.5	1.4	1.3	1.8

[a] LRS = likelihood ratio statistics.
[b] RR at 10 cigarettes per day.

statistically nonsignificant, such a sex difference in the dose response was also noted for lung cancer, and it is at least partially attributable to the sex difference in smoking: it is more common for women to puff, use low tar and filtertip cigarettes, and start smoking at a relatively older age. However, for gastric cancer, the interactive effects between smoking and other lifestyles, including dietary habits, may be related to the observed sex difference of the dose response.

The association of liver cancer with smoking, independent of drinking, was reported in several case-control studies (*5–7*) and was also confirmed by this analysis as well as by a recent case-control study in Japan (*8*). The extent to which the observed sex difference in mortality from cancers of the esophagus and liver can be attributed to drinking habits, as well as a possible interaction between smoking and drinking, is now being analyzed.

Most of the cancer of the uterus identified in this study can be judged to be cancer of the uterine cervix because

Table 5. Risk of lung cancer associated with cigarette smoking by daily cigarette consumption and follow-up intervals in males.

Cigarettes smoked	1966–1969		1970–1973		1974–1977		1978–1981	
	Number	Rate[a]	Number	Rate	Number	Rate	Number	Rate
Never smoked	10	12	20	26	28	41	15	26
1–4	4	65	2	37	3	65	5	134
5–14	55	41	79	65	101	92	106	114
15–24	60	35	118	76	193	136	241	192
25–34	10	58	10	63	26	181	30	235
35+	2	28	5	77	12	203	21	405

[a] Crude rate per 10^5 person-years.

Table 6. Relative risk of lung cancer associated with cigarette smoking by cigarette consumption and follow-up interval in males.

Cigarettes smoked	1966–1969		1970–1973		1974–1977		1978–1981	
	RR[a]	95% CI[a]	RR	95% CI	RR	95% CI	RR	95% CI
Never smoked	1.0[b]	—	1.5	0.7– 3.3	1.7	0.8– 3.6	0.9	0.4– 2.1
1–4	5.0	1.4–14.9	2.0	0.3– 7.6	2.6	– 8.6	4.6	1.4–13.1
5–14	4.1	2.2– 8.5	4.4	2.4– 9.1	4.5	2.5– 9.3	4.6	2.5– 9.3
15–24	4.6	2.5– 9.5	6.5	3.6–13.2	8.1	4.5–16.3	8.8	4.9–17.7
25–34	8.5	3.5–20.7	6.0	2.5–14.7	11.7	5.8–25.4	11.1	5.6–24.0
35+	3.8	0.6–14.4	6.7	2.1–19.0	12.2	5.3–28.9	18.2	8.8–40.4

[a] Relative risk (RR) and 95% confidence interval (95%CI) adjusted for attained age.
[b] Reference category.

Table 7. Risk of lung cancer associated with cigarette smoking by attained age and follow-up interval.

Attained age	RR[a] in			
	1966–1969	1970–1973	1974–1977	1978–1981
50–59	2.3	2.4	1.2	—
60–69	2.6	2.5	3.0	5.0
70–79	2.5	2.2	3.9	5.1

[a] Relative risk (RR) of lung cancer mortality at 10 cigarettes per day, obtained from a Poisson regression model, assuming a linear increase of RR with the daily cigarette consumption.

of the low incidence of cancer of the uterine corpus in Japan (*9*). A relationship between cigarette smoking and cancer of the cervix is yet to be established (*3*), but the recent findings of cotinine and nicotine, as well as smoking-related mutagenic activity in cervical mucus (*10,11*), supports the idea that there is a causal association between them. An elevation of the risk among smokers was observed in this study, but the dose response was not monotonic, suggesting a possible involvement of other factors. However, it is unlikely that the relationship is entirely attributable to a possible confounding between sexual behavior and smoking habits in women because of the sexual inactivity of Japanese females, particularly in the older generations.

The low relative risk of lung cancer associated with cigarette smoking, particularly in medium to heavy smokers, compared to that obtained in British physicians and other populations in Europe and the United States (*3,12*) is not limited to this six-prefecture cohort study; relatively low RRs were observed in other Japanese studies (*13–15*) that analyzed smoking-related lung cancer risk in the 1960s and 1970s by a case-control approach. However, as has been previously reported by Hirayama (*16*) and confirmed in this report, the RRs of lung cancer associated with cigarette smoking increased during the 16-year follow-up period, and the magnitude of RRs for the last 4-year interval (1978–1981) became similar to those obtained from the studies in Europe and the U.S. Relatively high RRs were also reported from recent case-control studies (*17–20*).

According to Doll and Peto (*12*), lung cancer incidence was proportional to the following function

$$(\text{cig} + 6)^2 \times (\text{age} - 22.5)^{4.5}$$

where cig is the amount of daily cigarette consumption and (age − 22.5) presumably corresponds to duration of smoking, while in our preliminary analysis (*4*) lung cancer mortality for a given cig was proportional to (duration of smoking)$^{4.4-4.6}$. The similarity of the coefficient for the log of duration of smoking is striking when the difference in lung cancer histology distribution in the two countries is taken into consideration. The lung cancer mortality for nonsmokers was unstable due to the small proportion of smokers, and it was estimated to be proportional to the power of 8.2 and 3.8 of the attained age in the follow-up intervals of 1966 to 1973 and 1974 to 1981, respectively (unpublished data). If the value can be assumed to be about 4.0, as reported by Doll and Peto and observed in this study for the latter half of the follow-up period, the RRs are a positive function of the attained age and will increase with advancement of the age of the cohort.

Although such an age-dependence of RRs of lung cancer associated with smoking apparently cannot explain the observed increase of RRs in the mid-1970s for all the birth cohorts, it should be noted that there was a sudden decrease of cigarette consumption in the 1940s. Since the turn of the century, the number of cigarettes consumed per adult per day increased gradually and reached about three cigarettes/adult/day before the be-

ginning of World War II. The consumption suddenly decreased at around the end of the war but started to increase in the 1950s (*21*). The shortage of cigarettes, which lasted 5 to 6 years after the war, and the subsequent rapid increase of cigarette consumption had virtually a similar effect on all the birth cohorts included in this six-prefecture cohort, in that they made them start cigarette smoking at the same calendar time (the early 1950s). The relatively smaller cumulative dose of cigarette smoking, especially among heavy smokers, made the RRs associated with smoking smaller than could be expected from the observations in Britain and the U.S. where such a shortage was not experienced (*22,23*).

According to Doll and Peto's formula, the RR for smokers can increase 2-fold as the duration of smoking increases from 20 to 30 years, and the change of RR with the duration of smoking becomes less evident for those who smoked longer (*24*). Therefore, the observed increase of RRs over the 16 years of follow-up period, which corresponds to 20 to 30 years since the cigarette shortage after the second World War is, to a large extent, explicable by the effect of the duration of smoking on the RRs of lung cancer associated with smoking. However, the improvement of diagnosis of lung diseases in recent years may also be related to it at least partially. The decrease of lung cancer mortality over the observation period, which was partially responsible for the increase of RRs in the 1978 to 1981 interval, as well as the fact that the most marked increase of the RRs was observed among farmers suggested an involvement of a change in diagnostic accuracy over the years. Watanabe et al. pointed out the change in the accuracy of diagnosis as an explanation for lung cancer mortality in rural areas overtaking the mortality in urban areas in the 1970s (*25*).

It should be noted that the prevalence of smokers in Japan changed over the years covered in this study, i.e., male smokers decreased from 82.7% in 1967 to 70.2% in 1980. Therefore, the actual duration of smoking was a little shorter than assumed in this analysis, but this will not affect the overall results significantly.

Summary

Reanalysis of the six-prefecture cohort study data using survival analysis based on Poisson regression models confirmed the previous results obtained from nonsurvival analysis and also shed a new light on the cancer mortality risk, including the dose-response relationships between the mortality risk and cigarette smoking, as well as their time trends. Further reanalysis of the data will deepen our understanding of the mortality experience of the six-prefecture cohort.

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